The Brain:
Cognitive Function and DM

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  • PTC Therapeutics, GSK Pharmaceuticals, Genzyme
  • NIH, MDA, National Ataxia Foundation
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Overview

• What cognitive and behavioral changes are seen in DM?

• What is the time course and cause of these changes?

• What are the underlying mechanisms leading to CNS change?

• What treatments are or will be available?

• What can you do to help conquer CNS effects of DM?
CNS Effects of Myotonic Dystrophy

- CNS Structure
- CNS Function
- Behavior
CNS is not Liver

CTG ↓
C/ CUG
↑
CCTG

CNS Structure
- White Mtr
- HippoCx
- Neuron
- Deep Nuclei
- Hypothal
- Frontal Cx
- Glia

CNS Function
- Dopamine
- Serotonin
- GABA
- LTP
- GluR
- Na
- Ca

Behavior
- Mood
- Executive
- IQ
- ADHD
- Personality
- Memory
- Sleep

CNS Structure
- Static
- Progressive
- Variable/
- Fluctuating
So what cognitive change occurs in DM?
What Clinical CNS Changes occur DM?

- Neuropsychological Abnormalities
  - Attention Deficit - (Douniol …Guile, Dev Med Child Neurol, 2012)
  - Developmental cognitive impairment (Wozniak, NMDisorders, 2012)
  - Executive function loss (DM1/DM2 – Meola, Neurology, 1999)
  - Avoidant personality (Winblad, NMDisorders, 2005).
  - Progressive loss of executive function (Modoni, JNeurol, 2008)

- Central motor function
  - Parkinsonism (Sansone, JNNP, 2006)

- Sleep Control
  - Sleep related ventilatory dysfunction
  - Central Hypersomnia (Ciafaloni, Neurology, 2008)

- Episodic encephalopathy? Seizures?

- Personal, Familial,Societal Impact of DM (Gagnon, JRehab Med, 2007)
So what multisystemic features contribute to DM CNS change?
DM1 Phenotype

Localization

- Skeletal Muscle
- Brain
- Heart
- Eye
- Endocrine
- Gut
- Skin
- Blood
How do DM Muscle changes inform us about DM CNS changes?
DM1 Phenotype

Pathological Mechanism

Developmental
Degenerative
Physiologic
Hormonal
Cardiovascular
Metabolic
Neoplastic
Inflammatory

Localization

Skeletal Muscle
Brain
Heart
Eye
Endocrine
Gut
Skin
Blood
How does DM time course affect understanding, investigation and treatment?
Time course of strength in Ctrl v DM1?

Normal

Birth Adult Mature

Development Composite Fluctuation

DM1

Birth Adult Mature Aged

Development Composite Degeneration

Fluctuation includes Δ in: stamina, sleepiness, pain, systemic disease
Time course of myotonia in DM1?

Birth | Adult | Mature | Aged

Development of Myotonia

Composite

Fluctuation
Time course of DM1 CNS Effects

- Development
- Fluctuation
- Composite
- Degeneration

Fluctuation includes Δ in: stamina, sleepiness, pain, systemic disease

DM1 Global CNS Effects

Birth | Adult | Mature | Aged

DM1 Specific Functional CNS Effect

Birth | Adult | Mature | Aged
What are structural CNS changes in DM?
Structural MRI Changes in DM

Kornblum, et al, J. Neurol, 2004
Diffusion Tensor Imaging (DTI)
Whole cerebrum white matter DTI

- Mean Diffusivity is significantly higher in DM1 vs. Controls
  - The differences are bilateral
  - Mean whole-brain diff: $F=41.7$, $p=0.000017$, effect size $(d)=2.72$, 8.4% diff
  - Mean right hemisphere diff: $F=42.1$, $p=0.000016$, effect size $(d)=2.66$, 8.8% diff
  - Mean left hemisphere diff: $F=39.7$, $p=0.000024$, effect size $(d)=2.72$, 8.0% diff
- This strongly suggests a significant abnormality in tissue organization/integrity
Dilated Perivascular Spaces in WM
Intracytoplasmic Inclusions
Mild frontal lobe gliosis
Neuropathology of DM

- White matter rarefaction in the cerebral hemispheres
- Increased space around blood vessels
- Minimal evidence of less than normal nerve cell numbers
- Neurofibrillary tangles of tau proteins
- Protein inclusion bodies in some deep brain regions
Freesurfer Cortical Parcellation identifies 35+ ROIs on cortical surface

We then evaluate the white matter in close proximity to these regions

Dependent measures in these analyses are mean FA or MD within the ROI

The data clearly demonstrate that these effects are NOT regional

- Ex: very large effects in caudal middle frontal, orbitofrontal, superior frontal, lateral frontal, inferior & superior parietal, inferior & middle temporal, lateral occipital, pre- and post-central, etc…
Automated tract analyses: DTI

- Inferior longitudinal fasciculus (dark blue): significant; $p = .00002$
- Superior longitudinal fasciculus (light blue): significant; $p = .00001$
  - Uncinate fasciculus (red): significant; $p < .00001$
- Occipitofrontal fasciculus (brown): significant; $p < .0001$
  - Cingulum (green): significant; $p = .00005$
- Corticospinal tracts (yellow): significant; $p = .00012$
- Corpus callosum (not shown): all significant but splenium
CNS Functional Abnormalities in DM
Behavioral CNS Changes in DM

- Neuropsychological Abnormalities
  - Impaired DM1 cognitive abilities noted in 1913
  - Apathy or avoidant personality
  - Progressive loss of executive function
- Central motor function
  - Parkinsonism
- Sleep Control
  - Sleep related breathing issues
  - Central Hypersomnia
- Personal, Familial and Societal Impact of DM
White matter integrity is highly related to cognitive functioning
Are there functional consequences of tract abnormalities?
Tractography and fMRI
CNS Molecular Phenotype in DM

Jiang, et al., HMG, 2004

Jiang, et al., HMG, 2004
Conclusions

• Many of DM multisystemic features affect the CNS
• Many DM CNS deficits appear to be more functional (physiological? pharmacological?) than structural
• The same “RNA mechanism” that affects skeletal muscle affect the brain
• Minor initial deficits can grow into major problems if not addressed
• Treat what’s treatable – other organ systems, sleep deficits, attention abnormalities, mood
Conclusions

• Much of CNS in DM is grossly normal - ? A good sign?

• An integrated and longitudinal explanation of function (neuropsychological, sleep, central motor control) and structure (imaging and pathology) is still needed.

• As Tee said more than 15 years ago: “Functional imaging strategies in reference to autopsy findings should provide important data to characterize the brain DM phenotype”
How You Can Help Fight DM

- Participate in MDF
- Register with the National DM Registry
- Participate in MDA
- Participate in research studies
- Set up tissue donation from surgeries or autopsy